EUROIMMUN US

510(k) SUMMARY

JUL 15 2013

A. 510(k) Number:

K131185

B. Purpose for Submission:

New device

C. Measurand:

Anti-Nuclear Antibodies

D. Type of Test:

Qualitative enzyme immunoassay

E. Applicant:

EUROIMMUN US INC.

F. Proprietary and Established Names:

EUROIMMUN ANA Screen ELISA (IgG)

G. Regulatory Information:

1. Regulation section:

   21 CFR 866.5100 – Anti-Nuclear Antibody immunological test system

2. Classification:

   Class II

3. Product code:

   LJM

4. Panel:

   Immunology

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H. Intended Use:

1. Intended use(s):

   The EUROIMMUN ANA Screen ELISA (IgG) is intended for the qualitative determination of IgG class antibodies against nuclear antigens (mixture of dsDNA, histones, ribosomal P-proteins, rRNP/Sm, Sm, SS-A, SS-B, Scl-70, Jo-1 and centromeres) in human serum and plasma (EDTA, Liheparin, Citrate). It is used as an aid in the diagnosis of mixed connective tissue diseases (MCTD), systemic lupus erythematosus, Sjögren's syndrome, progressive systemic sclerosis and polymyositis and dermatomyositis, in conjunction with other laboratory and clinical findings.

2. Indication(s) for use:

   Same as intended use.

3. Special conditions for use statement(s):

   For prescription use only.

4. Special instrument requirements:

   Microwell plate reader capable of measuring OD at 450nm and at 620nm for dual wavelength readings.

I. Device Description:

The EUROIMMUN ANA Screen ELISA (IgG) consists of a microwell ELISA plate coated with a mixture of dsDNA, histones, ribosomal P proteins, nRNP/Sm, Sm, SS-A, SS-B, Scl-70, Jo-1 and centromeres antigens, calibrator, positive and negative control, peroxidase-labeled anti-human IgG conjugate, sample buffer, wash buffer concentrate, TMB chromogen/substrate solution and stop solution.

J. Substantial Equivalence Information:

1. Predicate device name(s):
   Aesku Aeskulisa ANA Hep-2

2. Predicate 510(k) number(s):
   K081104

3. Comparison with predicate:

Similarities		
Item	Device	Predicate
Intended Use	Detection of IgG antibodies to nuclear antigens	Same
Assay Format	Qualitative	Same
Technology	ELISA	Same
Assay Platform	96-well microtiter plates	Same
Calibration	Relative evaluation	Same
Conjugate	Anti-human IgG labeled with horseradish peroxidase	Same
Substrate	TMB	Same
Procedure	Sample incubation with micro-well antigen coated plate, followed by a wash step, incubation with an anti-human IgG enzyme conjugate; wash step, incubation with substrate; then the addition of a stop solution and reading at 450nm.	Same
Reported Results	OD Ratio	Same
Cut-Off Level	Ratio 1.0	Same

Differences		
Item	Device	Predicate
Antigen Mixture	dsDNA, histones, ribosomal P proteins, nRNP/Sm, Sm, SS-A, SS-B, Scl-70, Jo-1, centromeres	dsDNA, histones, SS-A (Ro), SS-B (La), Sm, snRNP/Sm, Scl-70, Jo-1 and centromeric antigens and lysed HEp-2 cells
Calibrators & Controls	1 calibrator 2 controls: 1 positive, 1 negative	3 controls: 1 positive, 1 cut-off (used for calculation of results), 1 negative
Sample Buffer	Ready for use	5x concentrate
Wash Buffer	10x concentrate	50x concentrate
Stop Solution	0.5 M sulphuric acid	1 M hydrochloric acid
Sample Types	Serum or plasma (EDTA, Li-heparin, Citrate)	Serum
Sample Dilution	1:201	1:101

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K. Standard/Guidance Document Referenced (if applicable):

Guidance for Industry and FDA Staff: Recommendations for Anti-Nuclear Antibody (ANA) Test System Premarket (510(k)) Submissions (January 22, 2009)

L. Test Principle:

Patient samples are diluted 1:201 in sample buffer, 100 µl of each diluted patient sample and pre-diluted controls and calibrator are added to the antigen mixture coated microtiter wells and incubated for 30 minutes at room temperature. After incubation the microtiter well strips are washed with wash buffer to remove unbound antibodies and 100 µl of the anti-human IgG enzyme conjugate reagent is added to each microtiter well. After an additional 30-minutes incubation at room temperature, the microtiter wells are again washed 3 times with 300 µl of wash buffer to remove any unbound enzyme conjugate and 100 µl of the chromogen substrate is added. The strips are incubated for 15 minutes at room temperature and 100 µl stop solution is added. The microtiter plates are placed in an ELISA reader and read at a wavelength of 450 nm and a reference wavelength of between 620 nm and 650 nm within 30 minutes.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

The reproducibility of the test was investigated using sera with different concentrations. Intra-assay reproducibility is based on 20 determinations and inter-assay reproducibility on 30 determinations performed in 10 different runs on 5 days with 2 runs per day, each run performed with 3 replicates according to the package insert. The following results were obtained:

Intra-Assay Reproducibility

n = 16 - 20	ANA Screen ELISA (IgG) *Ratio*							
	Sample 1	**Sample 2**	**Sample 3**	**Sample 4**	**Sample 5**	**Sample 6**	**Sample 7**	**Sample 8**
Mean Value (x):	0.3	0.9	1.1	2.5	6.1	7.4	0.1	2.4
Range of Values:	0.2 – 0.3	0.8 – 0.9	1.0 – 1.2	2.3 – 2.6	5.8 – 6.3	7.1 – 7.7	0.1 – 0.2	2.0 – 2.8
Expected Result:	Negative	Negative	Positive	Positive	Positive	Positive	Negative	Positive
% positive:	0%	0%	100%	100%	100%	100%	0%	100%
% negative:	100%	100%	0%	0%	0%	0%	100%	0%
	Sample 9	**Sample 10**	**Sample 11**	**Sample 12**	**Sample 13**	**Sample 14**	**Sample 15**	**Sample 16**
Mean Value (x):	4.3	1.0	3.2	2.2	5.6	2.3	2.2	4.3
Range of Values:	3.9 – 4.6	0.9 – 1.0	3.0 – 3.5	2.0 – 2.5	4.9 – 6.2	2.1 – 2.5	2.0 – 2.5	4.0 – 4.8
Expected Result:	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive
% positive:	100%	100%	100%	100%	100%	100%	100%	100%
% negative:	0%	0%	0%	0%	0%	0%	0%	0%
	Sample 17	**Sample 18**	**Sample 19**	**Sample 20**	**Sample 21**	**Sample 22**		
Mean Value (x):	1.6	7.4	2.0	4.6	2.0	8.1		
Range of Values:	1.4 – 1.8	6.8 – 7.8	1.8 – 2.2	4.2 – 5.0	1.9 – 2.1	7.4 – 8.8		
Expected Result:	Positive	Positive	Positive	Positive	Positive	Positive		

n = 16 - 20	ANA Screen ELISA (IgG) *Ratio*							
	Sample 1	**Sample 2**	**Sample 3**	**Sample 4**	**Sample 5**	**Sample 6**	**Sample 7**	**Sample 8**
% positive:	100%	100%	100%	100%	100%	100%		
% negative:	0%	0%	0%	0%	0%	0%		

Inter-Assay Reproducibility

n = 30	ANA Screen ELISA (IgG) *Ratio*							
	Sample 1	**Sample 2**	**Sample 3**	**Sample 4**	**Sample 5**	**Sample 6**	**Sample 7**	**Sample 8**
Mean Value (x):	0.6	0.9	1.1	2.7	6.0	7.6	0.2	2.4
Range of Values:	0.5 – 0.7	0.7 – 1.0	1.0 – 1.2	2.5 – 3.0	5.4 – 6.4	7.2 – 8.0	0.1 – 0.3	1.6 – 3.1
Expected Result:	Negative	Negative	Positive	Positive	Positive	Positive	Negative	Positive
% positive:	0%	0%	100%	100%	100%	100%	0%	100%
% negative:	100%	100%	0%	0%	0%	0%	100%	0%
	Sample 9	**Sample 10**	**Sample 11**	**Sample 12**	**Sample 13**	**Sample 14**	**Sample 15**	**Sample 16**
Mean Value (x):	4.1	1.0	2.8	1.7	4.7	1.9	1.7	4.0
Range of Values:	3.3 – 4.9	0.8 – 1.2	2.0 – 3.5	1.1 – 2.2	4.2 – 5.6	1.1 – 3.3	1.1 – 2.2	3.4 – 4.8
Expected Result:	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive
% positive:	100%	100%	100%	100%	100%	100%	100%	100%
% negative:	0%	0%	0%	0%	0%	0%	0%	0%
	Sample 17	**Sample 18**	**Sample 19**	**Sample 20**	**Sample 21**	**Sample 22**		
Mean Value (x):	1.4	6.9	2.3	5.2	2.1	8.5		
Range of Values:	1.1 – 2.0	5.7 – 8.0	1.6 – 2.7	3.0 – 6.6	1.8 – 2.6	6.9 – 9.8		
Expected Result:	Positive	Positive	Positive	Positive	Positive	Positive		
% positive:	100%	100%	100%	100%	100%	100%		
% negative:	0%	0%	0%	0%	0%	0%		

The lot to lot reproducibility was investigated during the validation and quality control of the kit using different lots with QC samples distributed over the measurement range. The following results were obtained:

Lot to Lot Reproducibility

3 lots x 2 runs* * n lots x 1 run*	ANA Screen ELISA (IgG) *Ratio*							
	Sample 1	**Sample 2**	**Sample 3**	**Sample 4**	**Sample 5**	**Sample 6**	**Sample 7**	**Sample 8**
n:	11**	11**	11**	6*	6*	6*	6*	6*
Mean Value (x):	0.15	2.9	7.1	0.2	2.1	3.7	1.1	3.1
Range of Values:	0.1 – 2.0	2.7 – 3.2	6.8 – 7.8	0.1 – 0.2	1.9 – 2.4	3.4 – 4.3	1.0 – 1.2	3.0 – 3.2
Expected Result:	negative	positive	positive	negative	positive	positive	positive	positive
% positive:	0%	100%	100%	0%	100%	100%	100%	100%
% negative:	100%	0%	0%	100%	0%	0%	0%	0%
	Sample 9	**Sample 10**	**Sample 11**	**Sample 12**	**Sample 13**	**Sample 14**	**Sample 15**	**Sample 16**
n:	6*	6*	6*	6*	6*	6*	6*	6*
Mean Value (x):	2.0	4.8	2.3	2.0	3.9	1.5	6.0	2.0
Range of Values:	1.5 – 2.3	4.4- 5.7	1.9 – 2.7	1.5 – 2.2	3.7 – 4.2	1.4 – 1.5	5.3 – 7.4	1.9 – 2.1
Expected Result:	positive	positive	positive	positive	positive	positive	positive	positive
% positive:	100%	100%	100%	100%	100%	100%	100%	100%
% negative:	0%	0%	0%	0%	0%	0%	0%	0%
	Sample 17	**Sample 18**	**Sample 19**					
n:	6*	6*	6*					
Mean Value (x):	6.0	1.9	8.5					
Range of Values:	4.4 – 6.8	1.8 – 2.0	8.1 – 8.7					
Expected Result:	positive	positive	positive					
% positive:	100%	100%	100%					

*3 lots x 2 runs ** n lots x 1 run	ANA Screen ELISA (IgG) *Ratio*							
	Sample 1	**Sample 2**	**Sample 3**	**Sample 4**	**Sample 5**	**Sample 6**	**Sample 7**	**Sample 8**
% negative:	0%	0%	0%					

b. *Linearity/assay reportable range:*

Not applicable.

c. *High Dose Hook Effect*

Potential for a high dose Hook effect is a phenomenon that is inherent with one step "sandwich" assay designs: Very high concentrations of antigen in the patient sample bind to all available sites - saturating them - on both the antibody-solid phase and the antibody-labeled conjugate and thereby prevent the "sandwich" formation. Under these conditions, the measured level of analyte may be significantly lower than the actual level present in the sample. The two-step immunoassay design of the ANA Screen ELISA (IgG) eliminates the adverse contribution of binding proteins, endogenous interfering substances and general matrix effects due to the extra wash step.

d. *Traceability, Stability, Expected values (controls, calibrators, or methods):*

A recognized standard or reference material for anti-nuclear antibodies is not available. Results of this assay are given in ratios. The reactivity of the ANA Screen ELISA (IgG) was verified using the CDC ANA reference panel.

e. *Detection limit:*

Not applicable.

f. *Analytical specificity:*

Cross-reactivity: The quality of the antigen mixture coated on the plates (containing the antigens nRNP/Sm, Sm, SS-A, SS-B, Scl-70, Jo-1, dsDNA, histones, ribosomal P-proteins and centromeres) ensures a high specificity of the ELISA. Cross reactivity was investigated using a total of 82 clinically and serologically characterized samples (10 celiac disease for antibodies against gliadin and tissue transglutaminase, 17 Wegener's granulomatosis for ANCA, 39 rheumatoid arthritis for antibodies against CCP and 16 infectious diseases antibody positive samples). All except of 2 samples were negative in the ANA Screen ELISA (IgG), so no cross reactivity is expected.

Interference: To investigate the influence from hemoglobin, triglycerides and bilirubin, 4 different specimens at different ANA concentrations (ratio 0.5 – 7.3) were spiked with potential interfering substances and were incubated with the test system. The recovery in relation to the unspiked sample without interferent was calculated. The individual recovery of the positive or borderline samples was within the range of

92 – 107 %. No significant interference was observed for concentrations of up to 1000 mg/dl for hemoglobin, 2000 mg/dl for triglyceride and 40 mg/dl for bilirubin. Furthermore, the influence from rheumatoid factor was investigated by spiking of 6 different speciments with a rheumatoid factor positive material (characterized nephelometrically). The recovery in relation to the original sample (not spiked) was calculated. The recoveries were found within 100 - 110%. No interference was observed with rheumatoid factor up to 500 IU/ml.

f. Assay cut-off:

Ratio 1.0

2. Comparison studies:

a. Method comparison with predicate device:

A comparison study was performed using 158 clinically characterized samples from patients (49 MCTD, 37 systemic lupus erythematosus, 37 Sjögren's syndrome, 19 systemic sclerosis, 16 myositis) and 132 from control groups (10 celiac disease, 17 Wegener's granulomatosis, 39 rheumatoid arthritis, 16 infectious disease and 50 healthy), obtained from different sources. The panel consisted of 101 men and 174 women (and 14 unknown). Age ranged from 7 to 87 years with an average age of 46 years (15 unknown). The samples were tested with the EUROIMMUN ANA Screen ELISA (IgG) and with the Aesku Aeskulisa ANA Hep-2 as the predicate device. The results are shown in the table below. The discrepant samples were from controls and one MCTD sample in the cut-off range.

n = 290		Predicate ELISA	
		positive	**negative**
EUROIMMUN ANA Screen ELISA (IgG)	**positive**	137	3
	negative	5	145

Negative Agreement	145	/	148	=	98.0%	95% C.I.:	94.2%	-	99.6%
Positive Agreement	137	/	142	=	96.5%	95% C.I.:	92.0%	-	98.8%
Overall Agreement	282	/	290	=	97.2%	95% C.I.:	94.6%	-	98.8%

b. Matrix comparison:

The usability of plasma was investigated using sample pairs each of serum and corresponding plasma (EDTA, Li-heparin, Citrate). Passing-Bablok regression was calculated for the comparison of serum to plasma. The regression equation is near the ideal correlation (intercept 0; slope 1.0) indicating equivalence of concentrations between serum and the corresponding plasma matrices. Coefficients of determination were found to be above 0.99 and %recovery compared to serum was in the range of 90 to 112 % (serum = 100 %).

	EDTA plasma	Li-heparin plasma	Citrate plasma
n	12	12	12
Regression Equation: (y = plasma, x = serum) 95% C.I. of intercept 95% C.I. of slope	y = 0.04 + 0.99 x -0.02 – 0.13 0.96 – 1.02	y = -0.04 + 1.00 x -0.10 – 0.01 0.98 – 1.03	y = -0.00 + 0.99 x -0.02 – 0.05 0.95 – 1.00
Coefficient of determination R^2	0.9988	0.9992	0.9990
Mean %recovery Range of %recovery	103 % 98 – 112 %	99 % 90 – 109 %	98 % 95 – 104 %

3. Clinical studies:

a. Clinical Sensitivity:

Clinical studies were performed in cooperation with different sites. In total 738 clinically characterized samples were investigated for anti-nuclear antibodies (IgG). The EUROIMMUN ANA Screen ELISA (IgG) showed an overall sensitivity of 72.5% (95% C.I.: 68.0 – 76.7%) and a specificity of 95.8% (95% C.I.: 92.9 – 97.7%). The results are shown in the table below. 95% C.I. are calculated by the exact method.

No.	Panel	n	ANA Screen ELISA (IgG)		
			positive	%	95% C.I.
1	Mixed connective tissue diseases	21	20	95.2%	76.2 – 99.9%
2	Systemic lupus erythematosus	213	156	73.2%	66.8 – 79.1%
3	Poly-/dermatomyositis	26	4	15.4%	4.4 – 34.9%
4	Systemic sclerosis	81	59	72.8%	61.8 – 82.1%
5	Sjögren's syndrome	88	72	81.8%	72.2 – 89.2%
	Total	429	311	72.5%	68.0 – 76.7%

b. Clinical specificity:

No.	Panel	n	ANA Screen ELISA (IgG)		
			negative	%	95% C.I.
6	Celiac disease	10	10	100.0%	69.2 – 100.0%
7	Wegener's granulomatosis	17	16	94.1%	71.3 – 99.9%
8	Rheumatoid arthritis	203	191	94.1%	89.9 – 96.9%
9	Other autoimmune diseases*	63	63	100.0%	94.3 – 100.0%
10	Bacterial/viral infections	16	16	100.0%	79.4 – 100.0%
	Total	309	296	95.8%	92.9 – 97.7%

*from the following groups: AIH (n = 8), PBC (n = 9), Grave's disease (n = 12), Hashimoto (n = 11), celiac disease (n = 11), Diabetes Type I (n = 12)

c. Other clinical supportive data (when a. and b. are not applicable):

Not applicable.

4. Clinical cut-off:

   See Assay Cut-Off.

5. Expected values/Reference range:

   The levels of ANA (IgG) were analyzed in a panel of 200 samples from apparently healthy blood donors (120 men and 80 women with an average age of 40 y; age range: 19 – 68 y). The results are shown in the table below.

n	200
Positives	6
Negatives	194
Prevalence	3.0%
	Ratio
Lowest Value	0.1
Highest Value	4.5
Mean Value	0.2
Std Deviation	0.40

Proposed Labeling:
The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

Conclusion:
The submitted information in this premarket notification is complete and supports a substantial equivalence decision.

Michael Locke — *Signature*

Michael Locke/Director of Regulatory Affairs — *Printed Name/Title*

July 15, 2013 — *Date*

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center – WO66-G609
Silver Spring, MD 20993-0002

July 15, 2013

EUROIMMUN US.INC
C/O MR. MICHAEL LOCKE
DIRECTOR, REGULATORY AFFAIRS
1100 THE AMERICAN ROAD
MORRIS PLAINS NJ 07960

Re: k131185
Trade/Device Name: ANA Screen ELISA (IgG)
Regulation Number: 21 CFR 862.1660
Regulation Name: Antinuclear Antibody Immunological Test System
Regulatory Class: II
Product Code: LJM
Dated: April 24, 2013
Received: April 26, 2013

Dear Mr. Locke:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulations (21 CFR Parts 801 and 809), please contact the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638 2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely yours,

Maria M. Chan -S

Maria M. Chan, Ph. D.
Director
Division of Immunology and Hematology Devices
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health

Enclosure

Indications for Use

510(k) Number (if known): k131185

Device Name: EUROIMMUN ANA-Screen ELISA (IgG)

Indications For Use:

The EUROIMMUN ANA Screen ELISA (IgG) is intended for the qualitative determination of IgG class antibodies against nuclear antigens (mixture of dsDNA, histones, ribosomal P-proteins, rRNP/Sm, Sm, SS-A, SS-B, Scl-70, Jo-1 and centromeres) in human serum and plasma (EDTA, Li-heparin, Citrate). It is used as an aid in the diagnosis of mixed connective tissue diseases (MCTD), systemic lupus erythematosus, Sjögren's syndrome, progressive systemic sclerosis and poly-/dermatomyositis, in conjunction with other laboratory and clinical findings.

Prescription Use X AND/OR Over-The-Counter Use _____
(Part 21 CFR 801 Subpart D) (21 CFR 807 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH; Office of In Vitro Diagnostics and Radiological Health (OIR)

Maria M. Chan -S

Division Sign-Off
Office of In Vitro Diagnostics and Radiological Health

510(k): k131185